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1.0	An isolated mammalian hematopoietic progenitor cell	At least the $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of US 2020/0291433 ("the '433 Publication") meet the recited limitation of "An isolated mammalian hematopoietic progenitor cell". Exemplary support: The '433 Publication describes multiple methods of use for the SNS23.2.B87.A1 and SNS23.B87.A1 recombinant vectors (collectively, the "SNS23 Vectors"), which include their use to transduce isolated hematopoietic stem cells ("HSCs") of mice and humans. For example, it states: "[0253] *The presently disclosed subject matter provides vectors* and delivery systems . . . *comprising the above-described expression cassettes*. *The vectors* and delivery systems *are suitable delivery vehicles for the stable introduction of globin gene (e.g., human β-globin) into the genome of a broad range of target cells* to increase the production of the globin protein (human β-globin protein) in the cell. . . . [0254] ***In certain embodiments, the vector is a retroviral vector (e.g., . . . a lentiviral vector) that is employed for the introduction or transduction of the above-described expression cassette into the genome of a host cell (e.g., a hematopoietic stem cell***, an embryonic stem cell . . . or a hemogenic endothelium cell). . . . [0284] Suitable transduced cells include, but are not limited to, stem cells, progenitor cells, and differentiated cells. ***As used herein, the term 'progenitor' or 'progenitor cells' refers to cells that have the capacity to self-renew and to differentiate into more mature cells***. Progenitor cells have a reduced potency compared to pluripotent and multipotent stem cells. Many progenitor cells differentiate along a single lineage, but may also have quite extensive proliferative capacity. [0285] In certain embodiments, the transduced cells are stem cells. Stem cells have the ability to differentiate into the appropriate cell types when administered to a particular biological niche, in vivo. A stem cell is an undifferentiated cell capable of (1) long-term self-renewal, or the ability to generate at least one identical copy of the original cell, (2) differentiation at the single cell level into multiple, and in some instance [sic] only one, specialized cell type and (3) of in vivo functional regeneration of tissues. *Stem cells*

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		are sub-classified according to their development potential as totipotent, pluripotent, multipotent and oligo/unipotent. As used herein, the term 'pluripotent' means the ability of a cell to form all lineages of the body or soma (i.e., the embryo proper). For example, embryonic stem cells are a type of pluripotent stem cells that are able to form cells from each of the three germs [sic] layers, the ectoderm, the mesoderm, and the endoderm. ***As used herein, the term 'multipotent' refers to the ability of an adult stem cell to form multiple cell types of one lineage. For example, hematopoietic stem cells are capable of forming all cells of the blood lineage, e.g., lymphoid and myeloid cells.*** [0286] . . . ***In certain embodiments, the transduced cells are hematopoietic stem cells (HSCs)***. ***HSCs give rise to committed hematopoietic progenitor cells (HPCs) that are capable of generating the entire repertoire of mature blood cells over the lifetime of an organism***. . . . ***When transplanted into lethally irradiated animals or humans, hematopoietic stem and progenitor cells can repopulate the erythroid, neutrophil-macrophage, megakaryocyte and lymphoid hematopoietic cell pool***. [0287] ***HSCs can be isolated or collected from bone marrow, umbilical cord blood, or peripheral blood.*** HSCs can be identified according to certain phenotypic or genotypic markers. ***For example, HSCs can be identified by . . . [the] presence of various antigenic markers on their surface, many of which belong to the cluster of differentiation series (e.g., CD34,*** CD38 . . .). ***In certain embodiments, the transduced cell is a CD34$^+$ HSC***." '433 Publ., [0253], [0254], [0284] to [0287] (italics and emphasis added). In addition, the '433 Publication specifically describes human primary CD34$^+$ cells being isolated and then transduced with the SNS23.2.B87 vector. It states, for example: "***Example 8: Human Primary CD34$^+$ Cells Transduced with Vectors Disclosed Herein*** [0356] ***Human primary CD34$^+$ cells were isolated by centrifugation on a gradient of Ficoll-Hypaque Plus density***. ***CD34$^+$ cells were purified by positive selection using separation columns and beads.*** *After one day of cytokine stimulation* ***the CD34$^+$ were transduced with SNS23.2.B87.A1*** or TNS9.B87.A1 *vectors disclosed herein using 4 different MOI*. 10 and 15 days after transduction, the cells were harvested and the Vector copy number (VCN) was measured using the methods disclosed in Example 6. ***As shown in Table 3, at MOIs from 20x1 to 100x1, a linearly increased VCN response was observed in cells transduced with SNS23.2.B87.A1 vector, with a maximum VCN>2***. By contrast, cells transduced with TNS9.B87.A1 vector did not exhibit proportional increases in VCN at MOIs from 20x1 to 100x1. ***Unlike TNS9.B87.A1***

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vector, the SNS23.2.B87.A1 vector resulted in an increased globin gene transduction in CD34$^+$ cells up to >2 VCN per cell (2.33 at MOI 100, day 15, Table 3)."

'433 Publ., at [0356] (italics and emphasis added).

Table 3 from the '433 Publication is reproduced below, with the sections pertaining to the SNS23.2.B87.A1 vector highlighted in yellow.

TABLE 3

Transduction of human primary CD34+ cells

Groups	MOI	VCN day10	VCN day15
SNS23.2.B87.A1	10 x 1	1	0.21
Concentrate virus	20 x 1	1.78	0.56
	40 x 1	3.35	0.86
	100 x 1	7.33	2.33
TNS9.B87.A1	10 x 1	0.47	0.38
Concentrate virus	20 x 1	0.52	0.44
	40 x 1	0.48	0.40
	100 x 1	0.60	0.44
UT	NA	0.00	0.00

.

'433 Publ., at [0356] (emphasis added).

A Person of Ordinary Skill in the Art ("POSA") would understand, based on the above disclosures of the '433 Publication and general knowledge, that the CD34$^+$ cells isolated in Example 8 comprised a mixture of both hematopoietic stem cells (HSCs) and of hematopoietic progenitor cells (HPCs). For example, a 2014 scientific publication by Sidney *et al*. teaches that:

> "In clinical practice, ***CD34 expression*** is evaluated to ensure rapid engraftment in BM [bone marrow] transplants and ***can also be used as a selective marker in cell sorting*** *to enrich a population of immature hematopoietic cells*[46, 47]. ***Although sometimes assumed to be solely a stem cell marker, the detection of CD34 in BM or blood samples represents a hematopoietic stem/progenitor mix, of which the majority of cells are progenitor***.[44]"

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		Sidney *et al*., 2014, *Concise Review: Evidence for CD34 as a Common Marker for Diverse Progenitors*, Stem Cells, Vol. 32: 1380-1389 at 1381 (emphasis added) (citing reference 44 - Majeti *et al*., 2007, *Identification of a hierarchy of multipotent hematopoietic progenitors in human cord blood*, Cell Stem Cell, Vol. 1: 635-645).
1.1	or an isolated mammalian stem cell comprising	At least the $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meet the recited limitation of "or an isolated mammalian stem cell comprising". Exemplary support: *See* claim 1.0, *supra*. A POSA would understand, based on the disclosures of the '433 Publication and general knowledge that the isolation of $CD34^+$ cells prior to transduction with the SNS23 Vectors (*e.g*., as described in Example 8 of the '433 Publication) would necessarily also include the isolation of hematopoietic stem cells (HSCs), which are a type of mammalian stem cells.
1.2	a recombinant lentiviral vector	At least the $CD34^+$ hematopoietic stem cells and hematopoietic progenitor cells described in Example 8 of the '433 Publication meet the recited limitation of comprising "a recombinant lentiviral vector" because they were transduced with vectors SNS23.B87.A1 and SNS23.2.B87.A1 (collectively, the "SNS23 Vectors"), each of which is "a recombinant lentiviral vector". Exemplary support: *See* claims 1.0 and 1.1, *supra*. U.S. Patent No. 8058061 ("the '061 Patent") defines "recombinant lentiviral vector" as follows: "As used in the specification and claims hereof, the term 'recombinant lentiviral vector' refers to an artificially created polynucleotide vector assembled from a lentiviral-vector and a plurality of additional segments as a result of human intervention and manipulation." '061 Patent, at col. 2: 39-43.

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		The '433 Publication discloses that the subject matter of the 10/188221 patent application includes recombinant lentiviral vectors for use in transducing hematopoietic stem cells and hematopoietic progenitor cells so that they might produce human globin protein. For example, it states: "[0034] The presently disclosed subject matter also provides *recombinant vectors comprising the above-described expression cassettes*. ***In certain embodiments, the recombinant vector is a retroviral vector. In certain embodiments, the retroviral vector is a lentivirus vector***. . . . . . . [0265] While the manufacturing aspects of all retroviral vector types follow the same general principles, γ-retroviral**,** ***lentiviral*** and spumaviral ***vectors differ in some of their intrinsic biological properties.*** Gamma-retroviruses, including the prototypic murine leukaemia viruses (MLV), effectively infect many cell types but are unable to integrate in cells that do not proceed to S phase soon after infection. ***In contrast, lentiviruses and their vector derivatives can transduce nondividing cells*** *(Follenzi & Naldini, 2002; Salmon & Trono, 2002)* ***owing to their ability to translocate to the nucleus and integrate in the absence of cell division*** *(Lewis & Emerman, 1994; Goff, 2001)*. . . . [0266] These three vector systems differ in their integration patterns. The integration pattern of retroviruses is semi-random and biased towards genes and their vicinity in approximately two-thirds of all integration events (Schroder et al., 2002; Wu et al., 2003; Mitchell et al., 2004; De Palma et al., 2005; Trobridge et al., 2006). There are however subtle and possibly significant differences in their exact distribution. Gamma-retroviruses have a propensity to integrate upstream of transcribed genes, ***whereas lentiviruses and lentiviral vectors target the entire transcribed gene sequence.*** Foamy vectors appear to be less prone to intragenic integration (Trobridge et al., 2006). ***In certain embodiments, the vector comprising the expression cassette is a lentivirus vector***. The vectors can be derived from human immunodeficiency-1 (HIV-1), human immunodeficiency-2 (HIV-2), simian immunodeficiency virus (SIV), feline immunodeficiency virus (Hy), bovine immunodeficiency virus (BIV), Jembrana Disease Virus (JDV), equine infectious anemia virus (EIAV), caprine arthritis encephalitis virus (CAEV) and the like**.** ***In one non-limiting embodiment, the lentiviral vector is an HIV vector. HIV-based constructs are the most efficient at transduction of human cells***." [0286] . . . ***In certain embodiments, the transduced cells are hematopoietic stem cells (HSCs). HSCs give rise to committed hematopoietic progenitor cells (HPCs) that are capable of generating the entire***

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		repertoire of mature blood cells over the lifetime of an organism. . . . ***When transplanted into lethally irradiated animals or humans, hematopoietic stem and progenitor cells can repopulate the erythroid, neutrophil-macrophage, megakaryocyte and lymphoid hematopoietic cell pool***." '433 Publ., at [0034], [0265]-[0266] and [0286] (italics and emphasis added). In addition, the '433 Publication specifically describes the SNS23.2.B87.A1 vector as a lentiviral globin vector, and provides its underlying DNA sequence: "***Example 6: Generation of Globin Vectors*** Methods and Materials [0342] ***Vector Production*** [0343] ***Various lentiviral vectors were produced, including . . . SNS23.2.B87.A1. . . . The nucleotide sequence[] of . . . SNS23.2.B87.A1 . . . [is] set forth in . . . SEQ ID NO: 39 . . . .***" '433 Publ., at [0342] and [0343] (italics and emphasis added). *See also* '433 Publ., at Figures 14 and 15. A POSA would know, based on the disclosures of the '433 Publication and general knowledge, plus the similarity between the structures and DNA sequences of the SNS23.B87.A1 and SNS23.2.B87.A1 vectors, that both are recombinant lentiviral vectors.
1.3	which comprises a nucleic acid encoding a functional globin	The following recombinant lentiviral vectors meet the limitation "which comprises a nucleic acid encoding a functional globin": SNS23.B87.A1 and SNS23.2.B87.A1. <u>Exemplary support</u>: "The term 'functional globin gene' refers to a nucleotide sequence the expression of which leads to a globin that does not produce a hemoglobinopathy phenotype, and which is effective to provide therapeutic benefits to an individual with a defective globin gene." '061 Patent, at col. 2:44-48. "The functional globin gene may encode a wild-type globin appropriate for a mammalian individual to be treated, or it may be a mutant form of globin, preferably one which provides for superior properties, for example superior oxygen transport properties. *The functional globin gene includes both exons and introns, as*

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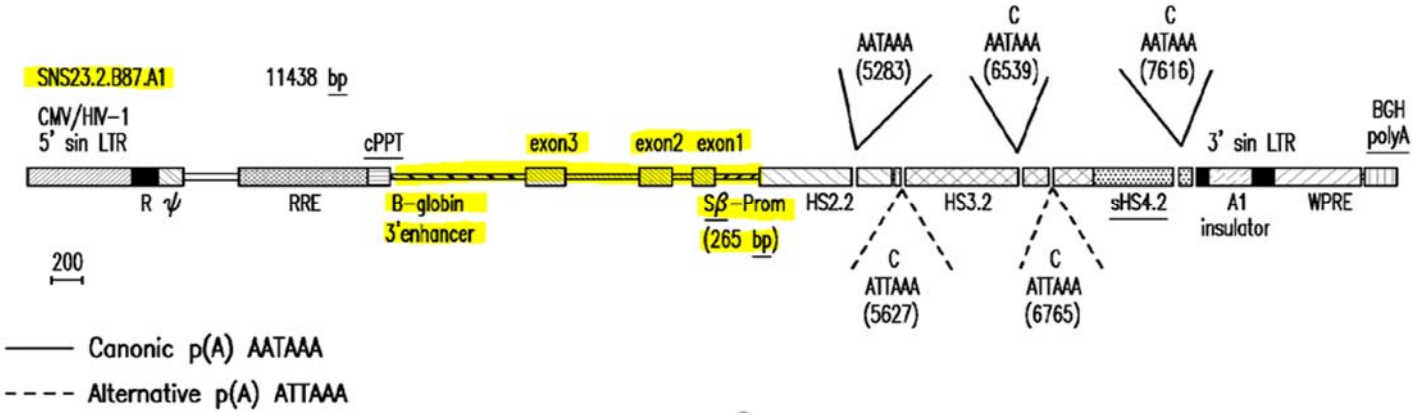
well as globin promoters and splice donors/acceptors. Suitably, the globin gene may encode α-globin, β-globin, or γ-globin. β-globin promoters may be sued [sic] with each of the globin genes." '061 Patent, at col. 2:48-56 (italics added).

The SNS23.B87.A1 and SNS23.2.B87.A1 vectors each encode a functional globin, as each vector contains within it β-globin exons 1 to 3, β-globin introns 1 and 2, plus a β-globin promoter and enhancer. Two figures from the '433 Publication (Figures 14 and 15) demonstrate these features and have been partially reproduced below, with their globin-related features highlighted in yellow.

The excerpt below from Figure 14 demonstrates that the SNS23.2.B87.A1 vector has β-globin exons 1, 2 and 3, β-globin introns 1 and 2, as well as a β-globin 3' enhancer. SNS23.2.B87.A1 is also shown with the 265 base-pair ("265 bp") β-globin promoter, Sβ-Prom.



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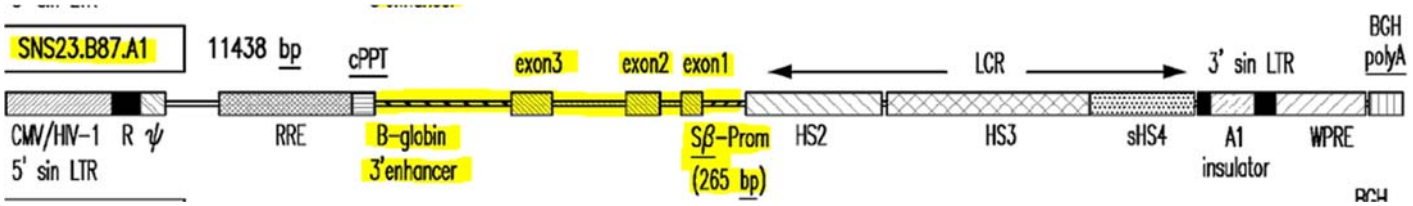
		The excerpt below from Figure 15 demonstrates that the SNS23.B87.A1 vector has β-globin exons 1, 2 and 3, β-globin introns 1 and 2, the β-globin 3' enhancer, and the 265 base-pair β-globin promoter, Sβ-Prom.  The SNS23.B87.A1 and SNS23.2.B87.A1 vectors (*e.g.*, Figs. 14-15) possess well-known control regions for human β-globin such as exons 1, 2, and 3, introns 1 and 2, and a β-globin enhancer and promoter, as described in the '061 Patent, at col. 2:52-54; accordingly, a POSA would understand both of these vectors comprise "a nucleic acid encoding a functional globin." The '433 Publication also provides additional information regarding the functionality and therapeutic usefulness of the β-globin produced by the SNS23.2.B87.A1 vector. See, for example, Figures 16 and 20, as shown on the following pages. The information specific to the SNS23.2.B87.A1 vector in these two figures has been highlighted in yellow.

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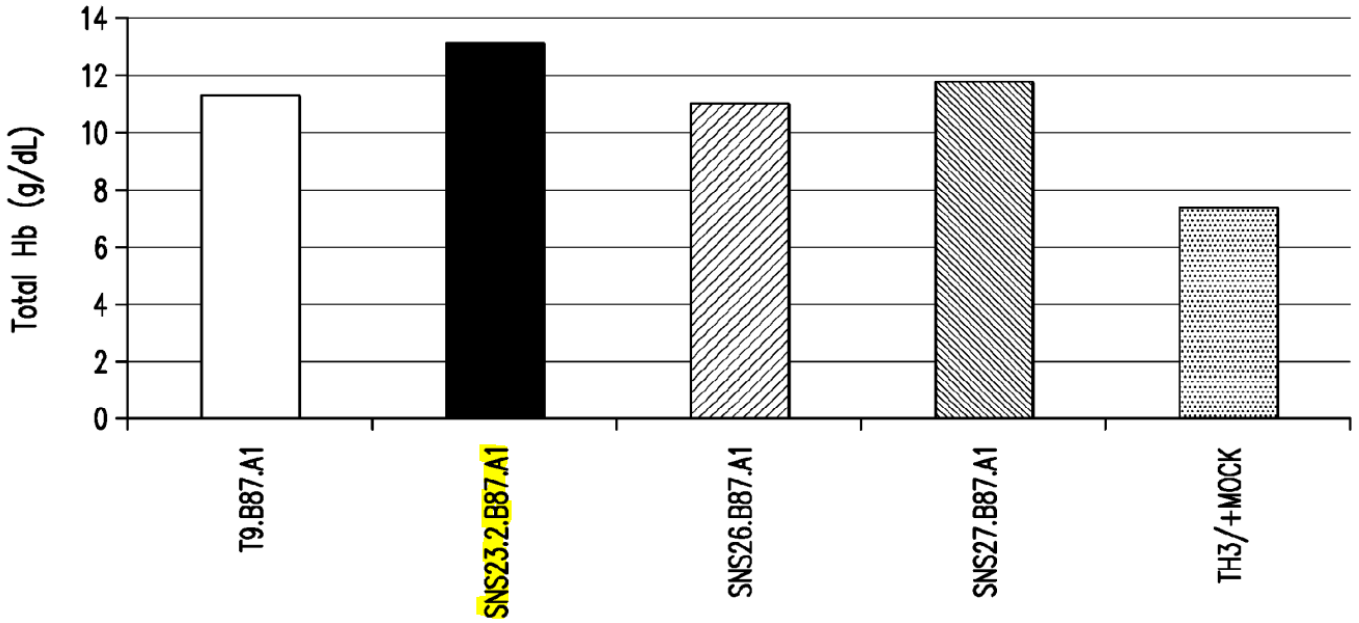
"FIG. 16 depicts the average Hb production for vectors (TNS9.B87.A1, *SNS23.2.B87.A1*. . . ."
'433 Publ., at [0059] (italics added).



Average of total Hb: (TNS9.B87.A1 n=4, SNS23.2.B87.A1 n=5 SNS26.B87.A1=5 SNS27.2.B87.A1=5 TH^{3}/$^{+}$mock n=1)

FIG. 16

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	"FIG. 20 depicts the average gain in Hb level (ΔHb) normalized to vector copy (VCN) at time points of 6-week, 5-month, and 9-month. ΔHb=Hb level−7.5 (baseline level in thalassemic mice)." '433 Publ., at [0063].

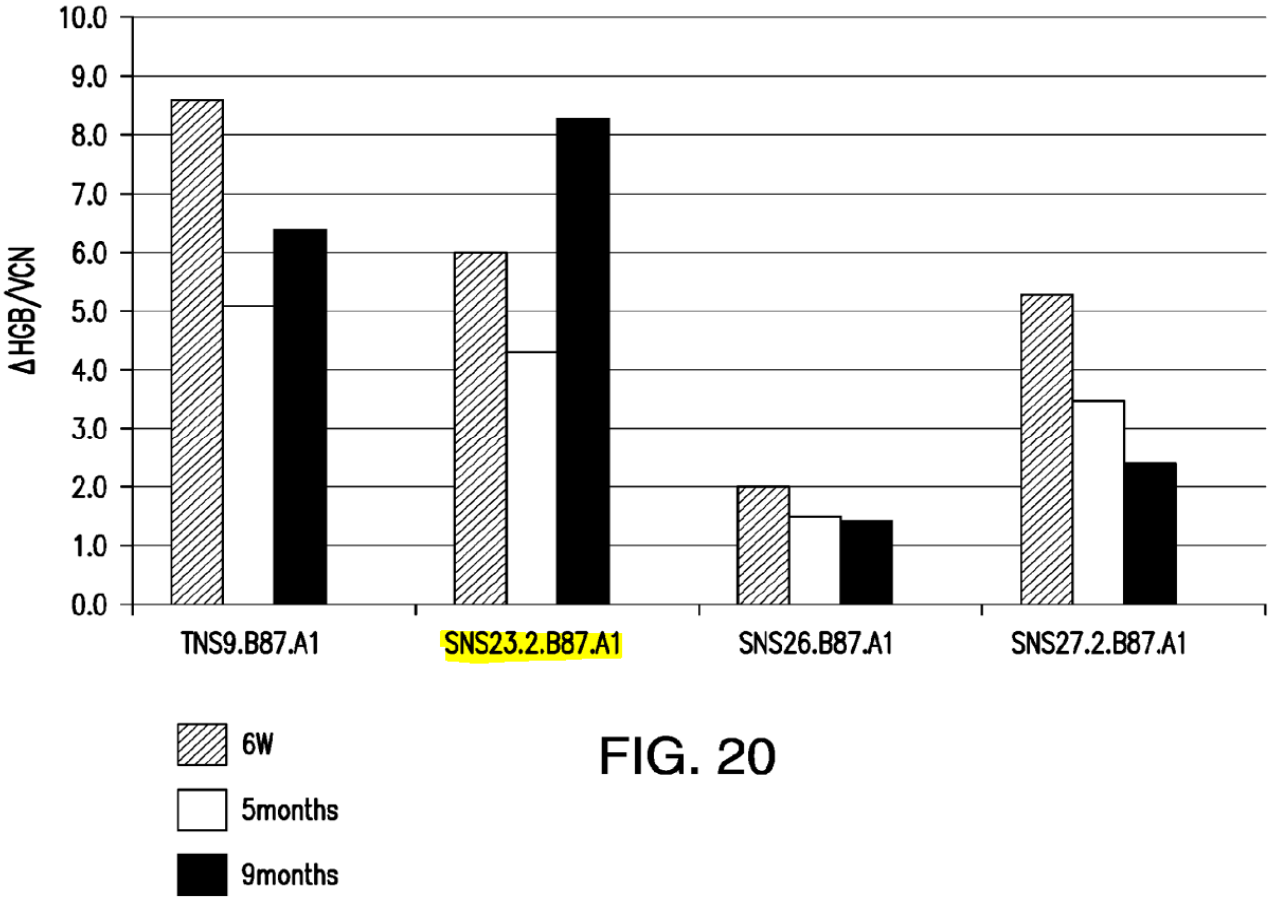

FIG. 20

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1.4	operably linked to a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human β-globin locus control region (LCR),	The SNS23.B87.A1 and SNS23.2.B87.A1 recombinant lentiviral vectors each meet the claim limitation of being "operably linked to a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human β-globin locus control region (LCR)". Exemplary support: Each of these vectors performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way (to obtain the same result): through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined. A Person of Ordinary Skill in the Art ("POSA") would read the information in May et al., *Therapeutic haemoglobin synthesis in β-thalassemic mice expressing lentivirus-encoded human β-globin*, Nature, Vol 406, pp. 82-86 (July 6, 2000) and the prosecution history for US Patent Application No. 10/188221[1], and understand them as indicating that the new vectors described therein (and claimed in the '179 patent) occupied a middle ground between the prior art vectors that contained minimal LCRs and the prior art vectors that contained much larger LCRs. For example, May 2000 states: "Incorporation of small elements spanning DNase HS2, HS3 and HS4 into viral vectors increases β-globin expression in mouse erythroleukaemia (MEL) cells[9,10]. *However, low-level expression, strong position effects and transcriptional inactivation are still observed in bone marrow chimaeras*[5,11]. Studies in transgenic mice[12] and deletional analyses[13] support the view that coordinated interaction of several genetic elements including the LCR is required for physiologic β-globin gene expression[12-15]. *We therefore thought that incorporation of large elements spanning HS2, HS3 and HS4*[16-18] *in a vector might enhance β-globin expression beyond levels previously achieved using arrayed minimal core elements*[5,9-11]*, and thus might diminish position effects and vector silencing. The efficient transduction of large genomic fragments using onco-retroviral vectors has proved to be severely curtailed by splicing and other alterations affecting the stability of the recombinant*

[1] US 8058061 claims priority to the patent application 10/188221 ("the '221 Application"), which issued as US 7541179 ("the '179 Patent"). Accordingly, this claim chart includes references to the specification of the '179 Patent and to the prosecution history of the '221 Application, as it also sheds light on the meaning of the '061 Patent claims.

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		genomes[9,10,16]. Here we report how these problems may be overcome by using vectors derived from human immunodeficiency virus 1, a retrovirus that has the ability to regulate packaging of unspliced viral genomes. We constructed two recombinant lentiviruses carrying β-globin transcription units (Fig. 1a, b). RNS1 contains a minimal LCR comprising previously tested core elements of HS2, HS3 and HS4 (ref. 9)." May 2000, at p. 82 (italics added). This contention is supported by multiple statements in the prosecution history of the '221 Application. For example, the Applicants stated: "The nature of the invention identifies the field of the endeavor - here a recombinant vector for treating hemoglobinopathies by expressing a functional globin in vivo using the claimed 3.2-kb portion of a human B-globin LCR. As an aside, ... the Examiner characterized the three fragments in the LCR as 'essential elements from the B-globin LCR.' Applicants wish to clarify this remark as it is not a term of art and is somewhat misleading. *The literature describes core HS sites as small fragments, and these core sequences might be considered as 'essential' or 'minimal' since they are the smallest fragments that can effect globin expression.* ***In point of fact, the present invention resides in having more than these small core sequences, namely, the invention resides in having the larger, specific HS-containing fragments in the vector and obtaining a level of globin expression not previously possible in vivo***." 09/12/2007 Rule 116 Amendment and Response for US Patent Application No. 10/188221, at p. 13 (hereafter "09/12/2007 Response") (italics and emphasis added). In fact, Applicants specifically pointed out to the USPTO Examiner for the '221 Application that prior art vectors had human β-globin LCR fragments that ranged in size from very large (20 kb) to very small (1 kb): "The human β-globin Locus Control Region was known to be a 20-30 kb region extending upstream from the start of the ε-globin gene, and the scientific literature had reported "a variety of expression studies with a 20-kb 'minilocus,' a 6.5-kb ['']microlocus' and a 1-kb fragment with core DNAse I hypersensitive site[s]." 09/12/2007 Response, at p. 10 (internal citations omitted). The Applicants distinguished their claims from the prior art by contending that, to their knowledge, "no previous studies have been conducted with a 3.2-kb portion of a human β-globin LCR as claimed herein." *Id.* Because the descriptions of the core sequences for the HS2, HS3 and HS4 regions were known in the prior art, the Applicants asserted that not only should one assume the DNAse hypersensitivity-spanning fragments "are *at*

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		least as big as their corresponding core sequences", but *"[i]n fact, one knows they must be larger*". 09/12/2007 Declaration of Jason W. Plotkin Under 37 C.F.R. §1.132 (hereafter, "Plotkin Declaration"), at ¶ 36 (italics added), as submitted with 09/12/2007 Response. A POSA would know that incorporation of only the "core" LCR fragments resulted in vectors with low viral titers that were "highly unstable with multiple rearrangements of the transferred proviral structures". *See* Negre *et al*., 2016, *Gene Therapy of the β-Hemoglobinopathies by Lentiviral Transfer of the βA(T87Q)-Globin Gene*, Human Gene Therapy, Vol. 27, No. 2, 148- 165 at 154 (hereafter, "Negre 2015"). In addition, a POSA would have been aware that "[r]educing the size of the LCR to minimal elements is unsatisfactory as β-globin expression levels are too low." *Id*. (citing references from 1992-1997); *see also*, May 2000, at p. 82. Accordingly, a POSA would understand that the claimed vectors needed to have an HS2-HS3-HS4 region that was bigger than 1 kb (*i.e*., had more than the minimal core HS sequences). In addition to setting a lower 1 kb boundary, the Applicants provided a flexible upper boundary of approximately 3.2 kb for the combined HS-spanning nucleotide fragments when they argued to the USPTO that: "The simple fact that the combination of the three HS-spanning fragments is 3.2 kb partially (and significantly) closes this aspect of the present claim, ***qualifies its size and thus provides the boundaries for ascertaining the elements excluded by use of "consisting essentially of" as the transistional phrase***. For example, any additional nucleotides added to the 3.2 kb fragment that cause the fragment to exceed 3.2 kb, would alter a basic and novel property of the invention. *As Applicants have exhaustively established on the record, the combined size of the three HS-spanning fragments so closely approximates 3.2 kb, that the number of additional nucleotides that could be added to (or removed from) this fragment is relatively few and non-material.* ***For example, the types of non-material nucleotide changes that can be accomodated are*** . . . ***adding a small linker to provide or change a restriction site, or making any other minor change to the sequence that does not alter the functionality of the fragment in driving globin expression, including changes at the ends of or at the junction points of the fragments***. All such changes are well known in the art and would be readily contemplated, accomplished and analyzed by skilled artisans. ***However, none of these non-material changes rises to the level of the fragments taught by Ryan or Antoniu. . . . Ryan shows only a 30-kb and a 22-kb recombinant nucleotide fragement that contain at least HS2, HS3, and HS4. . . . . . Antoniu show[s] only a single 5.5 kb nucleotide fragment that contains HS2, HS3 and HS4. Based on size, the Ryan and Antoniu fragments clearly differ from the 3.2 kb fragment of Claim 1***.

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		Further, based on nucleotide composition and arragement of the HS fragments (i.e., which pieces of the LCR are present), *neither Ryan nor Antoniu shows any fragment that combines the recited HS2-, HS3- and HS4-spanning fragments in contiguity into a single 3.2-kb fragment as claimed in present Claim 1*. Ryan's fragments are single, large restriction fragments from the LCR encomapassing all 5 HS sites in their natural order and sequence context. Antoniu fragments combine various restriction fragments which are larger and and distinct from those claimed by Applicants. Merely because the three HS fragments that Applicants have identified are within the sequence of the Ryan and Antonius fragments does not mean that those references "encompass" the claimed 3.2-kb fragment and thereby anticipate the present invention. ***The actual combination must be demonstrated ... and it is not, as evidenced by Applicants' use of "consisting essentially of" as the transitional phrase, along with bounding this operable LCR fragment at 3.2 kb, which, therefore, serve to distinguish the claimed invention from Ryan and Antonius as well as establish the basic and novel properties of this nucleotide fragment***." 12/03/2008 Amendment and Response After Final Office Action for US Patent Application No. 10/188221, at pp. 9-10 (italics and emphasis added). Thus, a POSA would understand, based on these comments in the prosecution history, that the claimed vectors in the '179 Patent can encompass vectors with LCR regions that differ in size and in sequence identity from the 3.2 kb LCR fragment disclosed in the Plotkin Declaration, provided that these differences do not bring the LCR fragment to a size that is much greater than 3.2 kb, or materially alter its function. "As apparent from the reference sequence, and as known in the art, ***the three fragments that form the 3.2-kb portion of the LCR are assembled from non-contiguous portions of the LCR***. In this regard, it should be recognized that these fragments can be joined in either 5'-3' or 3'-5' orientation using any of numerous techniques known to those of skill in the art to provide further vector examples. ***Once assembled into a vector, the fragments need not be cleavable nor must the entire restriction recognition site be present***. For example, one skilled in the art will readilty [sic] appreciate that the full restriction site might not be present if the fragment is blunt-ended before ligation, yet it may be present if the cut site is filled before ligation." 09/12/2007 Response, at pp.14-15 (italics and emphasis added). A POSA would also readily understand that sequence for a human gene, particularly a gene such as human β-globin, will change over time as sequencing techniques and technologies improve. Applicants admitted that the "globin genes were among the first ever sequenced at the nucleotide level." 9/12/2007 Response, at p. 7. Applicants themselves admitted in 2007 that "When accessing NG_000007 at present, one obtains version 3, which in relevant part includes an an additional approximately 9kb upstream of the version 1. ***Hence the numbering of the***

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		nucleotides is offset between the versions, and can be further slightly offset by polymorphisms and minor variations." *Id*. (italics and emphasis added). This, combined with the fact that the claim refers to "a" human β-globin LCR rather than "the" human β-globin LCR, would indicate to a POSA that it is the size of the HS-spanning fragments that is most important, and sequence variation in the HS-spanning LCR fragment of the claimed vectors is permitted, provided that it does not substantially alter the vector's properties. The '433 Publication discloses that each of the SNS23 Vectors is "operably linked" to a nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human β-globin locus control region (LCR)". For example, it states: "[0246] *SNS23.2.B87.A1, which comprises an expression cassette that comprises a human* $\beta^{A\text{-}T87Q}$ *globin gene, which is operably linked to a β-globin LCR* that comprises a 816 bp HS2 region e.g., one having the nucleotide sequence set forth in SEQ ID NO: 33), a 1301 bp HS3 region e.g., one having the nucleotide sequence set forth in SEQ ID NO: 34), and 754 bp HS4 region (e.g., one having the nucleotide sequence set forth in SEQ ID NO: 35); wherein the β-globin does not comprise a HS1 region; ... [0250] FIG. 15 shows five exemplary recombinant vectors *including . . . SNS23.B87.A1, which comprises an expression cassette that comprises a human* $\beta^{A\text{-}T87Q}$ *globin gene, which is operably linked to a β-globin LCR* that comprises a 816 bp HS2 region e.g., one having the nucleotides 45 to 860 of SEQ ID NO: 9), a 1301 bp HS3 region (e.g., one having the nucleotide sequence set forth in SEQ ID NO: 5), and 754 bp HS4 region (e.g., one having nucleotides 115 to 868 of SEQ ID NO: 6)...." *Id*., at [0246] and [0250] (italics added). Thus, from the '433 Publication and their general knowledge, a POSA would understand that: (1) The SNS23.B87.A1 vector has an LCR region that is made up of HS2, HS3 and HS4 fragments that total 2871 bp when combined: 816 bp HS2 fragment +1301 bp HS3 fragment + 754 bp HS4 fragment

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		Total = 2871 base pairs (2871 bp) As 1000 base pairs equal 1 kilobase (1 kb), 2871 bp equals 2.871 kb, which his falls within the permissible LCR range (greater than 1.0 kb and less than about 3.2 kb) that is defined by the prosecution history this claim; and (2) The SNS23.2.B87.A1 vector also has an LCR region that is made up of HS2, HS3 and HS4 fragments that when combined total 2871 bp: 816 bp HS2 fragment +1301 bp HS3 fragment + 754 bp HS4 fragment Total = 2871 base pairs (2871 bp), which as shown above is 2.871 kb. This total also falls within the permissible LCR range (greater than 1.0 kb and less than about 3.2 kb) that is defined by the prosecution history of this claim. *See id*., at [0246] and [0250] and Figures 14 and 15.
1.5	the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR,	The SNS23.B87.A1 and SNS23.2.B87.A1 recombinant lentiviral vectors each meet the claim limitation of "the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR". Exemplary Support: Each of these vectors performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way (to obtain the same result): through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined. As the Applicants explained in detail during prosecution of the '221 Application that matured into the '179 patent, the claimed vector "comprises a 3.2-kb portion of *a human β-globin locus control region (LCR)* ***consisting essentially of*** *3 restriction fragments*. Each fragment spans a particular DNase I hypersensitive site (HS) and each fragment's end is identified by particular restriction enzyme recognition sites (listed in 5' to 3' order)." 09/12/2007 Response, at p. 6 (italics and emphasis added).

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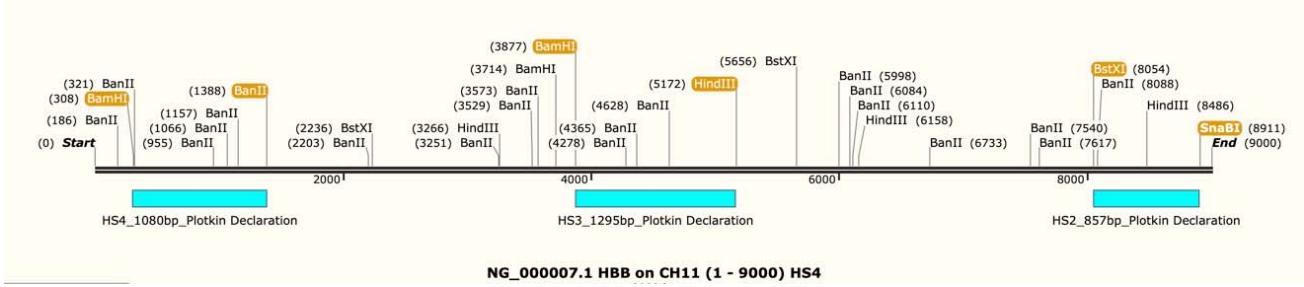
		The Applicants submitted the declaration of Mr. Jason Plotkin, a Research Assistant in one of the Inventor's labs (Dr. Michel Sadelain), which detailed how one could "identify and map the three recited restriction fragments based on the information in the specification, the scientific literature and the reference sequences available as of June 29, 2001," which is the earliest filing date of the '221 Application. This declaration used the NG000007.1 human β-globin reference sequence (hereafter, "NG7.1"). *See* Plotkin Declaration, ¶¶ 18 and 29. A POSA can take this same β-globin reference sequence (NG7.1) and use commonly available vector mapping software to map the HS fragments identified in Mr. Plotkin's Declaration onto its human β-globin LCR region. *See* Plotkin Declaration, at ¶¶ 38, 44 and 46, and the HS fragment map below:  The restriction sites recited in claim 1 and identified as bounding the three HS fragments are highlighted in orange (SnaBI, BstXI, HindIII, BamHI, Ban II and BamHI). The size of each originally-identified HS fragment is shown just beneath the blue box that marks its location within the NG7.1 sequence. A close-up view of this HS fragment map, which focuses on the far right region encompassing the HS2 fragment, is provided below:

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		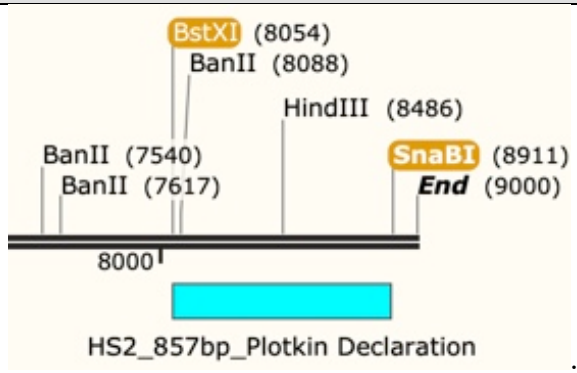 . The HS2 segment, represented by the blue box, is 857 base pairs in length. It is bordered by the SnaBI restriction enzyme recognition site on the right, and the BstXI restriction enzyme recognition site on the left. Based on the disclosures of the '061 Patent, '179 Patent, '433 Publication, and a POSA's general knowledge, a POSA would understand that the HS2 sequence within the SNS23.2.B87.A1 vector is equivalent to a "SnaBI and BstXI, HS3-spanning nucleotide fragment of said LCR", (*e.g.*, the HS2 fragment identified in the Plotkin Declaration), because it has the same function and performs this function in the same way to produce the same result – improved transcription of the neighboring β-globin gene within the vector. Likewise, since the SNS23 Vectors share the identical HS2 sequence, the same analysis applies to the SNS23.B87.A1 vector as well.
1.6	a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR,	The SNS23.B87.A1 and SNS23.2.B87.A1 recombinant lentiviral vectors each meet the claim limitation for "a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR". Exemplary Support: Each of these vectors performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way (to obtain the same result): through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined. As the Applicants explained in detail during prosecution of the '221 Application that matured into the '179 patent, the claimed vector "comprises a 3.2-kb portion of *a human β-globin locus control region (LCR)* ***consisting***

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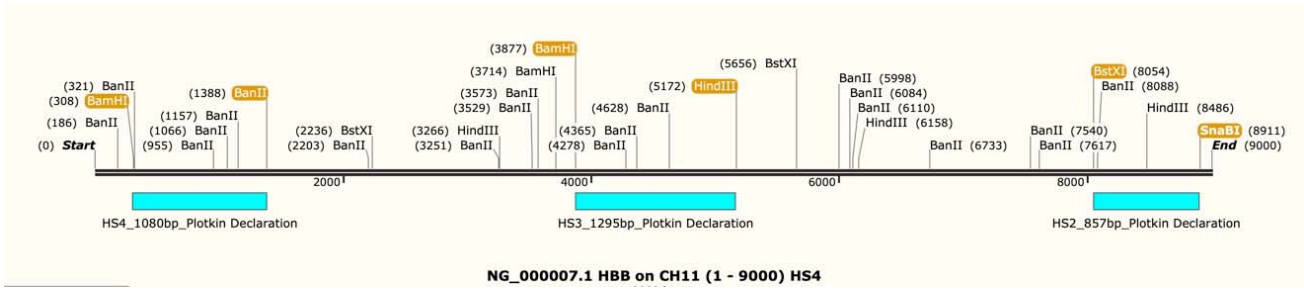
		essentially of *3 restriction fragments*. Each fragment spans a particular DNase I hypersensitive site (HS) and each fragment's end is identified by particular restriction enzyme recognition sites (listed in 5' to 3' order)." 09/12/2007 Response, at p. 6 (italics and emphasis added). The Applicants submitted the declaration of Mr. Jason Plotkin, a Research Assistant in one of the Inventor's labs (Dr. Michel Sadelain), which detailed how one could "identify and map the three recited restriction fragments based on the information in the specification, the scientific literature and the reference sequences available as of June 29, 2001," which is the earliest filing date of the '221 Application. This declaration used the NG000007.1 human β-globin reference sequence (hereafter, "NG7.1"). *See* Plotkin Declaration, at ¶¶ 18 and 29. A POSA can take this same β-globin reference sequence (NG7.1) and use commonly available vector mapping software to map the HS fragments identified in Mr. Plotkin's Declaration onto its human β-globin LCR region. *See* Plotkin Declaration, at ¶¶ 38, 44 and 46, and the HS fragment map below:  . The restriction sites recited in claim 1 and identified as bounding the three HS fragments are highlighted in orange (SnaBI, BstXI, HindIII, BamHI, Ban II and BamHI). The size of each originally-identified HS fragment is shown just beneath the blue box that marks its location within the NG7.1 sequence. A close-up view of this HS fragment map, which focuses on the middle region encompassing the HS3 fragment, is provided below:

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		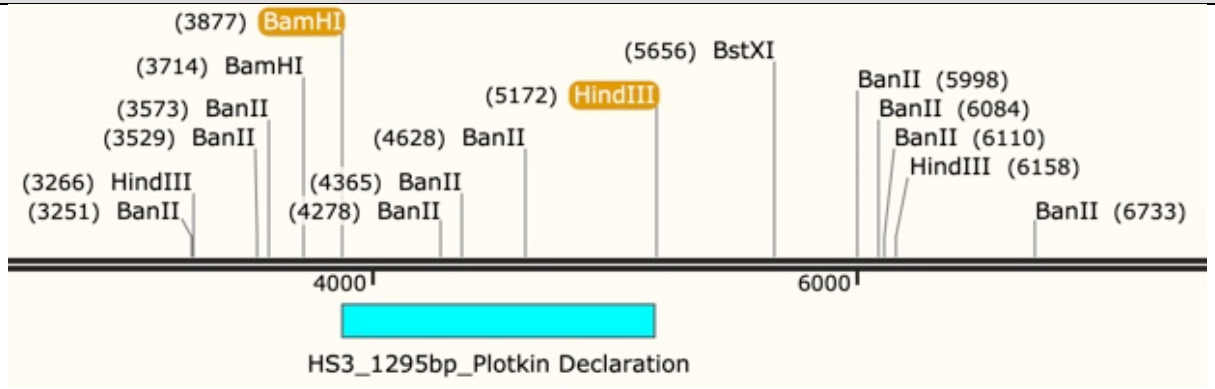 The HS3 segment, represented by the blue box, is 1295 base pairs in length. It is bordered by the HindIII restriction enzyme site on the right and the BamHI restriction enzyme site on the left. Based on the disclosures of the '061 Patent, '179 patent, '433 Publication, and a POSA's general knowledge, a POSA would understand that the HS3 sequence within the SNS23.2.B87.A1 vector is equivalent to "a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR", (*e.g.*, the HS3 fragment identified in the Plotkin Declaration), because it has the same function and performs this function in the same way to produce the same result – improved transcription of the neighboring β-globin gene within the vector. Likewise, since the SNS23 Vectors share the identical HS3 sequence, the same analysis applies to the SNS23.B87.A1 vector as well.
1.7	and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR,	The SNS23.B87.A1 and SNS23.2.B87.A1 recombinant vectors each meet the claim limitation "and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR". <u>Exemplary Support</u>: Each of these vectors performs the same function (enhancing β-globin expression beyond levels previously achieved), in the same way (to obtain the same result): through the incorporation of fragments of the HS2, HS3 and HS4 DNase I hypersensitive sites obtained from a human β-globin control region, which fragments are larger than the previously tested minimal HS core elements but smaller than about 3.2 kb when combined. As the Applicants explained in detail during prosecution of the '221 Application that matured into the '179 patent, the claimed vector "comprises a 3.2-kb portion of *a human β-globin locus control region (LCR)* ***consisting***

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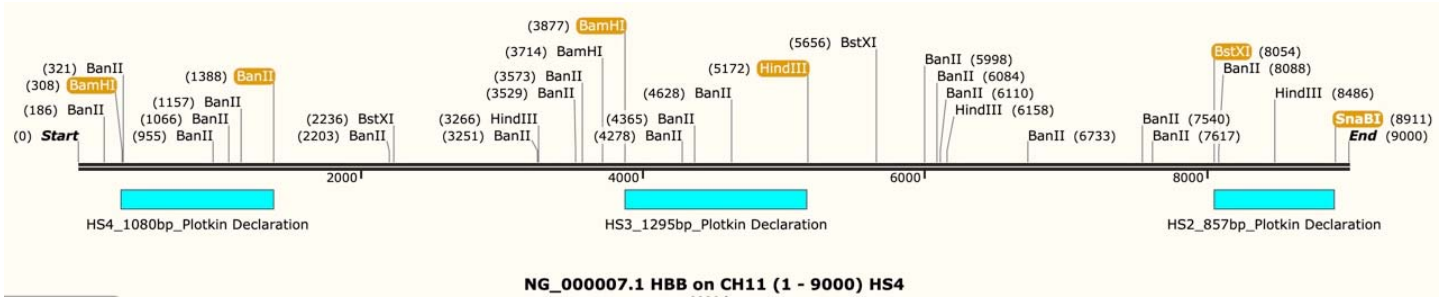
		essentially of *3 restriction fragments*. Each fragment spans a particular DNase I hypersensitive site (HS) and each fragment's end is identified by particular restriction enzyme recognition sites (listed in 5' to 3' order)." 09/12/2007 Response, at p. 6 (italics added) (emphasis added). The Applicants submitted the declaration of Mr. Jason Plotkin, a Research Assistant in one of the Inventor's labs (Dr. Michel Sadelain), which detailed how one could "identify and map the three recited restriction fragments based on the information in the specification, the scientific literature and the reference sequences available as of June 29, 2001," which is the earliest filing date of the '221 Application. This declaration used the NG000007.1 human β-globin reference sequence (hereafter, "NG7.1"). *See* Plotkin Declaration, at ¶¶ 18 and 29. A POSA can take this same β-globin reference sequence (NG7.1) and use commonly available vector mapping software to map the HS fragments identified in Mr. Plotkin's Declaration onto its human β-globin LCR region. *See* Plotkin Declaration, at ¶¶ 38, 44 and 46, and the HS fragment map below:  . A close-up view of this HS fragment map, which focuses on the far left region encompassing the HS4 fragment, is provided below:

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		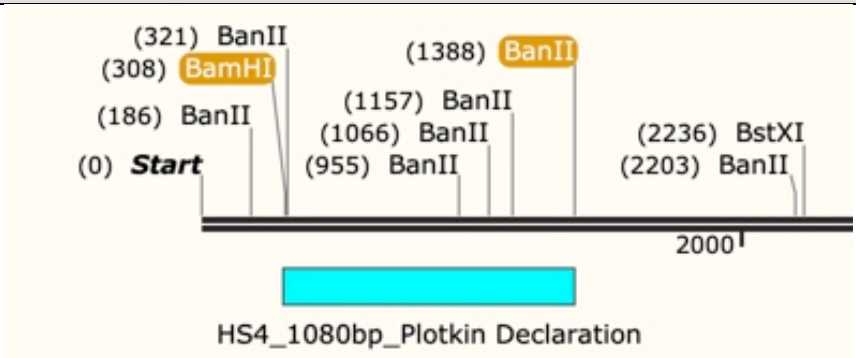 The HS4 segment, represented by the blue box, is 1080 base pairs in length. It is bordered by the BanII restriction enzyme site on the right and the BamHI restriction enzyme site on the left. Based on the disclosures of the '061 Patent, '179 patent, '433 Publication, and a POSA's general knowledge, a POSA would understand that the HS4 sequence within the SNS23.2.B87.A1 vector is equivalent to "a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR", (*e.g.*, the HS4 fragment identified in the Plotkin Declaration), because it has the same function and performs this function in the same way to produce the same result – improved transcription of the neighboring β-globin gene within the vector. Likewise, since the SNS23 Vectors share the identical HS4 sequence, the same analysis applies to the SNS23.B87.A1 vector as well.
1.8	said vector providing expression of the globin in a mammal in vivo.	The SNS23.B87.A1 and SNS23.2.B87.A1 recombinant lentiviral vectors each meet the claim limitation where "said vector providing expression of the globin in a mammal in vivo." Exemplary support: *See* claim 1.3 *supra*. *See also*, '433 Publication, at [0355] and Table 2, plus Figure 19 and [0062], which are all shown below. The information specific to vector SNS23.2.B87.A1 has been italicized or highlighted in yellow. "*Example 7: Evaluation of Globin Production at Different Time Points* [0355] *Additional experiments were conducted to measure the globin production at different time points in thalassemic mice transfected with vectors disclosed herein*. The methods used in Example 6 were applied in this Example. Average total Hb levels and average gains in Hb levels (ΔHb) in peripheral blood were

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measured in thalassemic mice transfected with vectors for 6-week, 5-month, or 9-month [sic]. ΔHb was normalized to vector copy (VCN), and ΔHb=Hb level-7.5 (baseline level in thalassemic mice, as all the time points consistently show an HGB value of 7.5 g/dL in the Thalassemic mice used as controls, [so] this value was used). *As shown in FIG. 19 and Table 2, globin production from all vectors, including SNS23.2.B87.A1, were stable over time. . . .*"

TABLE 2

Representative data for three different time points after transplant

Vectors	VCN	HGB (g/dL)	Δ(HGB-7.5)	ΔHGB/ copy
TNS9.B87.A1 (6 weeks)	0.5	10.6	3.8	8.6
TNS9.B87.A1 (5 months)	0.5	10.7	3.2	5.1
TNS9.B87.A1 (9 months)	0.4	9.8	2.3	6.4
SNS23.2.B87.A1 (6 weeks)	1.1	13.2	5.7	6.0
SNS23.2.B87.A1 (5 months)	1.1	11.3	3.8	4.3
SNS23.2.B87.A1 (9 months)	0.5	11.6	4.1	8.3
SNS26.B87.A1 (6 weeks)	2.0	11.2	3.7	2.0
SNS26.B87.A1 (5 months)	3.0	11.1	3.6	1.5
SNS26.B87.A1 (9 months)	3.1	11.1	3.6	1.4
SNS27.2.B87.A1 (6 weeks)	0.8	11.8	4.3	5.3
SNS27.2.B87.A1 (5 months)	1.5	12.1	4.6	3.5
SNS27.2.B87.A1 (9 months)	1.1	10.4	2.7	2.4
TH3/+ MOCK (6 weeks)	0	7.5	0	0
TH3/+ MOCK (5 months)	0	7.5	0	0
TH3/+ MOCK (9 months)	0	7.5	0	0

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Average of Vector copy number (VCN) in long-term hematopoietic chimeras. Average Hb level [g/dL] in peripheral blood (PB) of chimeric mice. ΔHb level was obtained by subtracting Th3/+ hemoglobin value (value=7.5 g/dL) from total Hb level for each animal tested. ΔHGb/copy=Correlation between delta (Δ)Hb and vector copy number. All the ΔHGb calculations are made using TH3/+ MOCK (7.5 g/dL) as basal HGB, value that is consistent in all the time points.

'433 Publ., at [0355] (Table 2 and legend) (italics and emphasis added).

See also Figure 19 of the '433 Publication, as reproduced below:

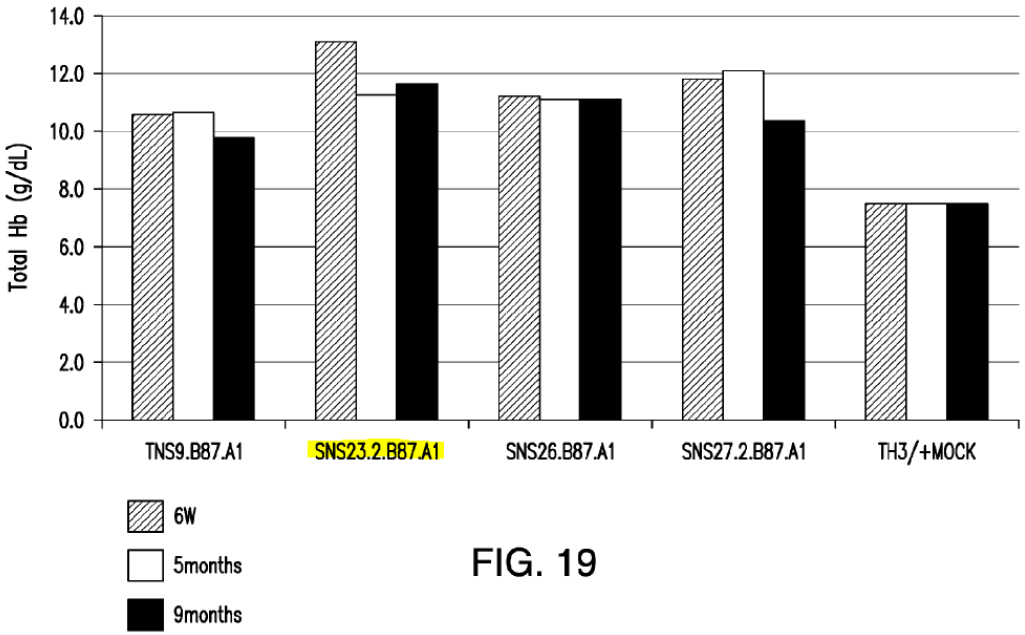

FIG. 19

"FIG. 19 depicts the average of total Hemoglobin (Hb) in thalassemic mouse peripheral blood at time points of 6-week, 5-month, and 9-month [sic]." '433 Publ., at [0062].

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2.0	The cell of claim 1,	At least the $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meet the recited limitations of claim 1. Exemplary support: *See* claim 1.0 to 1.8 *supra*.
2.1	wherein the mammalian hematopoietic progenitor cell or the stem cell is a human cell.	At least the $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meet the recited limitation "wherein the mammalian hematopoietic progenitor cell or the stem cell is a human cell." Exemplary support: The '433 Publication describes multiple methods of use for the SNS23.2.B87.A1 and SNS23.B87.A1 recombinant vectors (collectively, the "SNS23 Vectors"), which include their use to transduce isolated human hematopoietic stem cells ("HSCs") and isolated human hematopoietic progenitor cells ("HPCs"). For example, it states: "[0253] *The presently disclosed subject matter provides vectors* and delivery systems . . . *comprising the above-described expression cassettes*. *The vectors* and delivery systems *are suitable delivery vehicles for the stable introduction of globin gene (e.g., human β-globin) into the genome of a broad range of target cells* to increase the production of the globin protein (human β-globin protein) in the cell. . . . [0254] ***In certain embodiments, the vector is a retroviral vector (e.g., . . . a lentiviral vector) that is employed for the introduction or transduction of the above-described expression cassette into the genome of a host cell (e.g., a hematopoietic stem cell***, an embryonic stem cell . . . or a hemogenic endothelium cell). . . . [0284] Suitable transduced cells include, but are not limited to, stem cells, progenitor cells, and differentiated cells. ***As used herein, the term 'progenitor' or 'progenitor cells' refers to cells that have the***

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		capacity to self-renew and to differentiate into more mature cells. Progenitor cells have a reduced potency compared to pluripotent and multipotent stem cells. Many progenitor cells differentiate along a single lineage, but may also have quite extensive proliferative capacity. [0285] In certain embodiments, the transduced cells are stem cells. Stem cells have the ability to differentiate into the appropriate cell types when administered to a particular biological niche, in vivo. A stem cell is an undifferentiated cell capable of (1) long-term self-renewal, or the ability to generate at least one identical copy of the original cell, (2) differentiation at the single cell level into multiple, and in some instance [sic] only one, specialized cell type and (3) of in vivo functional regeneration of tissues. *Stem cells are sub-classified according to their development potential as totipotent, pluripotent, multipotent and oligo/unipotent*. As used herein, the term 'pluripotent' means the ability of a cell to form all lineages of the body or soma (i.e., the embryo proper). For example, embryonic stem cells are a type of pluripotent stem cells that are able to form cells from each of the three germs [sic] layers, the ectoderm, the mesoderm, and the endoderm. ***As used herein, the term 'multipotent' refers to the ability of an adult stem cell to form multiple cell types of one lineage. For example, hematopoietic stem cells are capable of forming all cells of the blood lineage, e.g., lymphoid and myeloid cells.*** [0286] . . . ***In certain embodiments, the transduced cells are hematopoietic stem cells (HSCs). HSCs give rise to committed hematopoietic progenitor cells (HPCs) that are capable of generating the entire repertoire of mature blood cells over the lifetime of an organism***. . . . ***When transplanted into lethally irradiated animals or humans, hematopoietic stem and progenitor cells can repopulate the erythroid, neutrophil-macrophage, megakaryocyte and lymphoid hematopoietic cell pool***. [0287] ***HSCs can be isolated or collected from bone marrow, umbilical cord blood, or peripheral blood.*** HSCs can be identified according to certain phenotypic or genotypic markers. ***For example, HSCs can be identified by . . . [the] presence of various antigenic markers on their surface, many of which belong to the cluster of differentiation series (e.g., CD34,*** CD38 . . .). ***In certain embodiments, the transduced cell is a CD34$^+$ HSC***." '433 Publ., [0253], [0254], [0284] to [0287] (italics and emphasis added). In addition, the '433 Publication specifically describes human primary CD34$^+$ cells being isolated and then transduced with the SNS23.2.B87 vector. It states, for example:

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"***Example 8: Human Primary CD34⁺ Cells Transduced with Vectors Disclosed Herein***

[0356] ***Human primary CD34⁺ cells were isolated by centrifugation on a gradient of Ficoll-Hypaque Plus density. CD34⁺ cells were purified by positive selection using separation columns and beads.*** *After one day of cytokine stimulation* ***the CD34⁺ were transduced with SNS23.2.B87.A1*** or TNS9.B87.A1 *vectors disclosed herein using 4 different MOI.* 10 and 15 days after transduction, the cells were harvested and the Vector copy number (VCN) was measured using the methods disclosed in Example 6. ***As shown in Table 3, at MOIs from 20x1 to 100x1, a linearly increased VCN response was observed in cells transduced with SNS23.2.B87.A1 vector, with a maximum VCN>2***. By contrast, cells transduced with TNS9.B87.A1 vector did not exhibit proportional increases in VCN at MOIs from 20x1 to 100x1. ***Unlike TNS9.B87.A1 vector, the SNS23.2.B87.A1 vector resulted in an increased globin gene transduction in CD34⁺ cells up to >2 VCN per cell (2.33 at MOI 100, day 15, Table 3)***."

'433 Publ., at [0356] (italics and emphasis added).

Table 3 from the '433 Publication is reproduced below, with the sections pertaining to the SNS23.2.B87.A1 vector highlighted in yellow.

TABLE 3

Transduction of human primary CD34+ cells

Groups	MOI	VCN day10	VCN day15
SNS23.2.B87.A1	10 x 1	1	0.21
Concentrate virus	20 x 1	1.78	0.56
	40 x 1	3.35	0.86
	100 x 1	7.33	2.33
TNS9.B87.A1	10 x 1	0.47	0.38
Concentrate virus	20 x 1	0.52	0.44
	40 x 1	0.48	0.40
	100 x 1	0.60	0.44
UT	NA	0.00	0.00

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		'433 Publ., at [0356] (emphasis added).
5.0	The cell of claim 1,	At least the $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meet the recited limitations of claim 1. Exemplary support: *See* claim 1.0 to 1.8 *supra*.
5.1	wherein said functional globin is a mutant globin.	At least the $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meet the recited limitations of claim 1 and the limitation "wherein said functional globin is a mutant globin." Exemplary support: *See* claim 1.3 *supra*. *See also*: "***3.2. Globin Gene*** [0193] *In accordance with the presently disclosed subject matter, the expression cassette comprises a globin gene or a functional portion thereof.* ***The globin gene can be a β-globin gene***, a γ-globin gene, or a δ-globin gene. ***In certain embodiments, the expression cassette comprises a human β-globin gene***. ***In accordance with the presently disclosed subject matter, the human β-globin gene*** can be a wild-type human β-globin gene, ***a deleted human β-globin gene comprising one or more deletions of intron sequences, or a mutated human β-globin gene encoding at least one anti-sickling amino acid residue.*** In certain non-limiting embodiments, a presently disclosed expression cassette comprises a wild-type human β-globin gene. A wild-type human β-globin gene comprises three exons (exon 1, exon 2, and exon 3). ***In certain embodiments, a presently disclosed expression cassette comprises a non-wild-type (mutated or modified) human β^A-globin gene.*** In certain embodiments, a presently disclosed expression cassette comprises a human β-globin gene with a deletion in intron 2 (IVS2). In certain embodiments, the deletion in IVS2 is about 370 bp. The deletion in IVS2 can eliminate AT-rich (ATR) sequences that comprise a cryptic polyadenylation site responsible of premature termination of the transcription. ***In certain***

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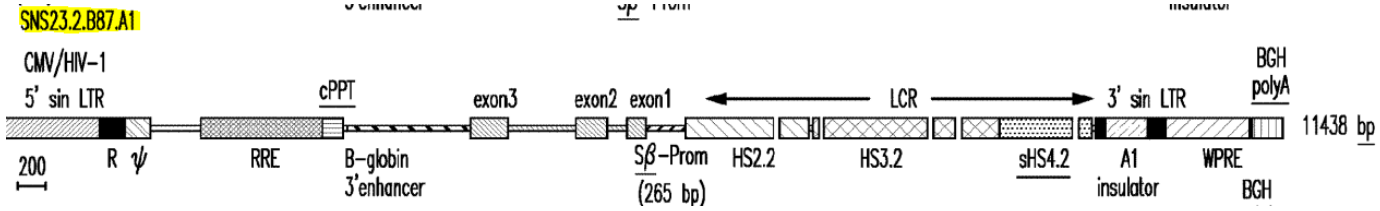
embodiments, a presently disclosed expression cassette comprises a human β^A-globin gene encoding a threonine to glutamine mutation at codon 87 (βA-T87Q). The glutamine residue at position 87 in the gamma-globin chain augments the anti-sickling activity of the gamma chain relative to the beta chain, while preserving adult oxygen-binding characteristics of the beta chain (Nagel et al., Proc. Natl. Acad. Sci. U.S.A. (1979); 76:670-672). ***In certain embodiments, a functional portion of a globin gene has at least about 80%, at least about 90%, at least about 95%, at least about 99% or at least about 100% identity to a corresponding wild-type reference polynucleotide sequence***.

[0194] ***In certain embodiments, the human β^A-globin gene is a human β^A-globin gene encoding a threonine to glutamine mutation at codon 87 ($\beta^{A\text{-}T87Q}$)***. In certain embodiments, the human β^A-globin gene encoding a threonine to glutamine mutation at codon 87 (βA-T87Q) further comprises a deletion in intron 2 (e.g., an about 370 bp deletion). ***In certain embodiments, the human β^A-globin gene encoding a threonine to glutamine mutation at codon 87 ($\beta^{A\text{-}T87Q}$) comprises the nucleotide sequence set forth in SEQ ID NO: 36, which is provided below***."

'433 Publ., at [0192]-[0194] (italics and emphasis added).

See also Figure 13 of the '433 Publication, and its accompanying descriptions in same, which show that the SNS23.2.B87.A1 recombinant lentiviral vector includes a mutant human β-globin gene. A portion of Figure 13 (showing the SNS23.2.B87.A1 vector) is reproduced below:



"[0245] ***FIG. 13 shows the following five exemplary recombinant vectors***. . . .

[0246] ***SNS23.2.B87A1, which comprises an expression cassette that comprises a human $\beta^{A\text{-}T87Q}$ globin gene***, which is operably linked to a β-globin LCR that comprises a 816 bp HS2 region (e.g., one having the

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		nucleotide sequence set forth in SEQ ID NO:33), a 1301 bp HS3 region (e.g., one having the nucleotide sequence set forth in SEQ ID NO:34), and a 754 bp HS4 region (e.g., one having the nucleotide sequence set forth in SEQ ID NO:35), wherein the β-globin LCR does not comprise a HS1 region. . . .” ’433 Publ., at [0245] and [0246] (italics and emphasis added). In view of these disclosures in the ’433 Publication and general knowledge, a POSA would readily understand that both SNS23 Vectors comprise a mutant human β-globin gene.
7.0	The cells of claim 1,	At least the $CD34^+$ hematopoietic stem cells (“$CD34^+$ HSCs”) described in Example 8 of the ’433 Publication meet the recited limitations of claim 1. Exemplary support: *See* claim 1.0 to 1.8 *supra*.
7.1	wherein said functional globin is a β-globin.	At least the $CD34^+$ hematopoietic stem cells (“$CD34^+$ HSCs”) described in Example 8 of the ’433 Publication meet the recited limitations of claim 1 and the limitation “wherein said functional globin is a β-globin.” Exemplary support: *See* claim 5.1 *supra*.
8.0	The cell of claim 7,	At least the $CD34^+$ hematopoietic stem cells (“$CD34^+$ HSCs”) described in Example 8 of the ’433 Publication meet the recited limitations of claim 7. Exemplary support: *See* claims 7.0 and 7.1, *supra*.
8.1	wherein said β-globin is a	At least the $CD34^+$ hematopoietic stem cells (“$CD34^+$ HSCs”) described in Example 8 of the ’433 Publication meet the recited limitations of claim 8.0, and the limitation “wherein said β-globin is a human β-globin.”

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	human β-globin.	Exemplary support: *See* claims 7.0 and 7.1, *supra*.
11.0	A method for making a mammalian hematopoietic progenitor cell or a mammalian stem cell composition which comprises	At least the method of making CD34+ hematopoietic stem cells ("CD34+ HSCs") described in Example 8 of the '433 Publication meet the limitation of "[a] method for making a mammalian hematopoietic progenitor cell or a mammalian stem cell composition which comprises". Exemplary support: *See* claims 1.0 to 1.8, *supra*.
11.1	(a) preparing a recombinant lentiviral vector comprising	At least the method of making CD34+ hematopoietic stem cells ("CD34+ HSCs") described in Example 8 of the '433 Publication meets the limitation of "(a) preparing a recombinant lentiviral vector comprising" because the SNS23.2.B87.A1 vector used therein was first prepared and then used in this example. Exemplary support: *See* claim 1.2, supra.
11.2	a nucleic acid encoding a functional globin	At least the method of making CD34+ hematopoietic stem cells ("CD34+ HSCs") described in Example 8 of the '433 Publication meets the limitation of "a nucleic acid encoding a functional globin" because the SNS23.2.B87.A1 vector used therein meets this limitation. Exemplary support:

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		See claim 1.3, supra.
11.3	operably linked to a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human β-globin locus control region (LCR),	At least the method of making CD34+ hematopoietic stem cells ("CD34+ HSCs") described in Example 8 of the '433 Publication meets the limitation of "operably linked to a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human β-globin locus control region (LCR)," because the SNS23.2.B87.A1 vector used therein meets this limitation. Exemplary support: *See* claim 1.4, *supra*.
11.4	the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR,	At least the method of making CD34+ hematopoietic stem cells ("CD34+ HSCs") described in Example 8 of the '433 Publication meets the limitation of "the three fragments being a BstXI and SnaBI, HS2-spanning nucleotide fragment of said LCR," because the SNS23.2.B87.A1 vector used therein meets this limitation. Exemplary support: *See* claim 1.5, *supra*.

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11.5	a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR,	At least the method of making CD34+ hematopoietic stem cells ("CD34+ HSCs") described in Example 8 of the '433 Publication meets the limitation of "a BamHI and HindIII, HS3-spanning nucleotide fragment of said LCR," because the SNS23.2.B87.A1 vector used therein meets this limitation. Exemplary support: *See* claim 1.6, *supra*.
11.6	and a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR,	At least the method of making CD34+ hematopoietic stem cells ("CD34+ HSCs") described in Example 8 of the '433 Publication meets the limitation of "a BamHI and BanII, HS4-spanning nucleotide fragment of said LCR," because the SNS23.2.B87.A1 vector used therein meets this limitation. Exemplary support: *See* claim 1.7, *supra*.
11.7	said vector providing expression of the globin in a mammal in vivo;	At least the method of making $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meets the limitation wherein "said vector providing expression of the globin in a mammal in vivo;" because the SNS23.2.B87.A1 vector used therein meets this limitation. Exemplary support: *See* claim 1.8, *supra*.
11.8	and (b) obtaining hematopoietic progenitor cells or stem cells from the	At least the method of making $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meets the limitation "and (b) obtaining hematopoietic progenitor cells or stem cells from the mammalian individual,". Exemplary support:

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	mammalian individual,	*See* claims 1.0, 1.1 and 1.8, *supra*.
11.9	and transducing the cells with the recombinant vector.	At least the method of making $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meets the limitation "and transducing the cells with the recombinant vector." Exemplary support: *See* claims 1.0, 1.1. and 1.8, *supra*.
15.0	The method of claim 11,	At least the method of making $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meets the limitations of claim 11. Exemplary support: *See* claims 11.0 through 11.9, *supra*.
15.1	wherein said functional globin is a human β-globin.	At least the method of making $CD34^+$ hematopoietic stem cells ("$CD34^+$ HSCs") described in Example 8 of the '433 Publication meets the limitations of claim 11 and the limitation "wherein said functional globin is a human β-globin." Exemplary support: *See* claims 11.0 through 11.9, *supra*.

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